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ROLE OF MACROPHAGE DERIVED CYTOKINES IN ARTICULAR CARTILAGE DESTRUCTION IN RHEUMATOID ARTHRITIS

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ABSTRACT

In recent years variety of proinflammatory and anti-inflammatory cytokines have been identified which are involved in pathogenesis and progression of rheumatoid arthritis (RA) in various extent. Macrophage derived cytokines and T cell cytokines having crucial role in the pathogenesis of RA. It is well established that imbalance between proinflammatory and anti-inflammatory cytokines triggers induction of autoimmunity and RA. However exact cytokine pathways that responsible for induction of inflammation and cartilage destruction are not fully cleared. The aim of this review article is to provide a detailed information about the role of various macrophage derived cytokines in the pathogenesis and progression of RA.

Keywords: Rheumatoid arthritis, cytokine, macrophage, cartilage

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune & inflammatory disorder that can affect synovial membrane of the synovial joints **[1]**. The most important hallmark of RA is inflammation & destruction of synovial membrane **[2]**. The most important Signs and symptoms are swelling of the joint, arthralgia, redness in the joint and reduction in the rate of movements if RA affects the knees **[1]**. It has been noted that early cases

of RA affect smaller joints first. Particularly the joints of the fingers of hands and fees are affected first. In the severe cases, the disease spread to the larger joints of knees, wrists, ankles, hips, elbows, and shoulders. The metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints of hands, the metatarsophalangeal (MTP) joints of the feet are the most commonly effected joints by RA. Interaction between synovial fibroblasts, T &B lymphocytes, macrophages and the inflamed synovial cells like plasma cells, macrophages and dendritic cells leads to synovial inflammation. These cells secrete various cytokines that responsible for interaction between these cells. During the inflammatory reactions, various proinflammatory cytokines like IL-1, IL-6, TNF-α are produced which responsible for inflammation of synovial membrane and cartilage destruction through the formation of hyperplastic fibroblast like synoviocytes (FLS) also known as pannus. Pannus releases proteolytic enzymes known as matrix metalloproteinases (MMPs) which destroys cartilage so that pannus invades inside the cartilage **[119]**. Apart from the matrix proteinase enzymes, mast cell proteases and cathepsin having important role in cartilage destruction **[120, 121]**. Fibroblastic pannus cell releases various factors that activate osteoclast to contribute increased resorption of bones **[122]**. Inflammatory cytokines inhibit mineralization of bones and differentiation of osteoblast cells which results in prevention of osteoblast activity **[123]**. In some people; the condition can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels **[2]**. It has been noted that about 20-30% peoples of RA having the airway problems like pulmonary fibrosis **[3]**. Lung diseases are more prevalent in males of RA who are smoker & previous history of lung disease **[4]**. A recent case study indicates that risk of cardiovascular diseases like vascular endothelium damage & early atherosclerosis are 2 times more in the patients of RA than the general population **[5]**. After 20 years of illness, RA patients have a 40 percent elevated risk of mortality relative to the general population **[124]**. Some persons with RA having ocular complications like fibrinoid necrosis, vascular occlusion & infiltration of neutrophils & macrophages which leads to deposition of immune complex, matrix metalloproteinases (MMPs) secretions, inflammatory cytokine formation & autoantibody formation **[6]**.

EPIDEMIOLOGY

1% of total world populations are affected by RA **[2]**. It prevalently affects women than the

men **[1]**. women have greater functional disability and pain than men **[30]**. According to global burden of disease study in the year 2010, it is estimated that 0.24 percent people worldwide effected by RA **[26]**. 0.5 to 1 percent peoples of united states of America & northern European countries are affected by RA **[27, 28]**. In united states & in northern European countries the annual incidence of RA is estimated to be 40 per 100,000 persons **[29]**.

ROLE OF MACROPHAGE DERIVED CYTOKINES IN RA

Cytokines plays an important role in RA. For better understanding, cytokines are divided into two groups: Proinflammatory cytokines & anti-inflammatory cytokines. Balance between proinflammatory & anti-inflammatory cytokines plays an important role in prevention of cartilage destruction in RA. Some cytokines like interleukin (IL-1) and tumor necrosis factor (TNF)-α increases inflammatory responses and responsible for destruction of cartilage. IL-15, IL-17, RANKL, IL-12, and 1L-18 etc are the T cell cytokine which have important role in inflammation of joints **[8]**. Other cytokines, such as IL-4, IL-13 and IL-10 act mainly as anti-inflammatory cytokines. In progressive RA the levels of anti-inflammatory cytokines are too low to neutralize the destructive effects of proinflammatory cytokines though anti-inflammatory cytokines are also present in the joints of RA **[31]**. During inflammatory reactions, monocyte & T lymphocytes migrates at the synovium from blood capillaries. Activated macrophages releases variety of cytokines among which IL-1 & TNF-α **[7]**. It is believed that IL-1 & TNF-α plays a crucial role in cartilage destruction in RA. TNFα is an inflammatory mediator, whereas IL-1 is a crucial cytokine in destruction of articular cartilage **[8]**. TNFα alone is not so much destructive, but it has some synergistic way that can enhance the destructive behavior of IL-1 **[8]**. T cells produces IL-15, IL-17, RANKL, IL-12, and 1L-18 which plays an important role as proinflammatory cytokines in RA **[8]**.

A. Role of IL-1 family cytokines in RA:

Several members of the IL-1 superfamily have been implicated in the pathogenesis of RA. 11 cytokines constitutes IL-1 superfamily constitute IL-1 family that shows significant participation in the progression and pathogenesis of RA. The members of IL-1 superfamilyare- IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra), IL-18, IL-33, IL-36 (α, β, γ, IL-36Ra), IL-37, IL-38Among of which IL-1α, IL-1β, IL-18, IL-33, IL-36(α, β, γ) are proinflammatory cytokines involved in

various inflammatory disorders whereas IL-1 receptor antagonist (IL-1Ra), IL-36 receptor antagonist (IL-36Ra), IL-37, IL-38 having anti-inflammatory effects **[13]**. IL-1α, IL-1β and natural IL-1 receptor antagonist (IL-1ra) are expressed widely in the synovium **[32]**. There are two types of IL-1 Receptors (IL-1R) are present. These are type I & type II IL-1 Receptors. IL-1R type I expressed in very low concentration in cells like fibroblast, endothelial cells & in T lymphocytes. IL-1R type I having the capacity of intracellular signaling because of long cytoplasmic tail **[34]**. IL-1R type II expressed in monocytes, B lymphocytes & in neutrophils. This type of IL-1R is not functionally active because of short cytoplasmic tail.

A.1. Role of IL-1α in RA:

IL-1α are proinflammatory cytokine which is initially available as 31kD precursor molecule known as pro-IL-1α. Pro- IL-1α is biologically active. IL-1 α is primarily bound to the membrane. Chondrocytes present in articular cartilage & responsible for the production and maintenance of the cartilage matrix. Pro-inflammatory cytokines like IL-1α upregulate the production of MMPs and to inhibit proteoglycan synthesis which causes loss of cartilage **[33]**.

A.2. Role of IL-1β in RA:

IL-1β independently as well as with other inflammatory mediators causes inflammatory & catabolic reactions in cartilage and various parts of joints. It is produced as precursor protein known as pro-IL-1β having 269 amino acids **[35, 36]**. Active form of IL-1β consist of 153 amino acid residues **[37]**. IL-1β produced from inactive precursor molecule pro-IL-1β by the enzyme Caspase 1or IL-1β converting enzyme or ICE by intracellular proteolysis. IL-1β then released into extracellular space **[37]**. The synthesis of IL-1β in joints are regulated by various cells like osteoblasts, synovial membrane cells, mononuclear cells that infiltrated in the structure of joints during inflammation **[38, 39]**. IL-1β binds to IL-1R1 receptor leads to recruitment of additional IL-1R3 chain which forms complex with the help of its intracellular portion Toll-IL-1R which further recruits the adapter protein known as MyD88 **[40]**. This entire complex binds to serine/threonine kinase enzymatic domain of IRAK (IL-1 receptor associated kinase signaling) which further activates TRAF6 which leads to further binding of TAB1, TAK1 & TAB2(41). IκB kinase complex phosphorylation done by TAK1 which further causes activation of transcription factor NF-$_K$B **[41]**. It also activatesc-Jun N-terminal kinase (JNK) and p38MAPK. **[41]**.

Activation of Transcriptional factors leads to expression of various genes encoding for cytokines, chemokines, enzymes, adhesion molecules & various inflammatory mediators **[42]**. IL-1β having Signiant role in the metabolism of extracellular matrix **[43]**. Many studies have been confirmed that IL-1β having numerous roles in the destruction of articular cartilage. Type-II collagen & aggrecan which are one of the important structural proteins of extracellular matrix are mainly produced by chondrocytes.IL-1β interfere the synthesis of type-II collagen & aggrecans so that formation of building blocks of extracellular matrix is inhibited **[44]**. Apart from the inhibition of the synthesis of building blocks of extracellular matrix, IL-1β increases the production of MMPs like MMP-1, MMP-3 & MMP-13 which mainly responsible for cartilage destruction **[45, 46]**. Apart from these MMPs, release of MMP-9 also stimulated by IL-1β **[62]**.

MMPs are the zinc dependent endopeptidases which are capable of degradation of extracellular matrix **[51]**. These enzymes are highly catabolic in nature & physiological expressions of genes encoding for MMPs are regulated very strictly. There are 5 types of MMPs have been identified: 1) collagenases (MMP-1, MMP8 & MMP-13), 2) Gelatinases A&B (MMP-2 & MMP-9 respectively), 3) stromelysins (MMP-3, MMP-10 & MMP-11) 4) membrane type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP24 & MMP-25), and 5) miscellaneous subgroup that includes MMP-7, MMP-11, MMP-12, MMP-20 & MMP-23. Genes encoding for MMPs are expressed mainly during wound healing& during development of embryo **[52, 53]**. Among these MMPs, MMP-1, MMP-13, MMP-2and MMP-14 are expressed constitutively in adult cartilage & having important role in tissue turnover **[54]**. Apart from these effects, MMPs also responsible for degradation of various extracellular components **[156]**. In normal joint, expression of collagenases, gelatinases A and B, stromelysins and membrane type MMPs are very low but their expression is increased in RA joints **[10, 157]**.

MMP-1 is also known as interstitial collagenase. Under normal conditions, expression of MMP-1is low. The expression of MMP-1 occurs during endochondral bone formation, metaphysis & diaphysis of long bones. During metaphysis & diaphysis MMP-1 is mainly produced by osteoblast & hypertrophic chondrocytes **[51]**. Upregulation of MMP-1 expression occurs in RA & responsible for degradation of type I, type II & type III collagen **[55]**. However, it

has been noted that MMP-1 shows most destructive activity against type III collagen. The MMP-1 expression level is 10 times greater than the MMP-13 expression level **[57]**.

MMP-3 is also known as stromyelin-1 & are normally absent in the joint tissues.MMP-3 levels increased in the joint tissue during osteoarthritis & RA which results in degradation of collagen type II, IV, III, IX and X, laminin, elastin etc. **[51]**. MMP-3 also acts as a transcription factor and upregulate the expression of other MMPs **[58]**. Apart from these effects, MMP-3 also activates proMMP-1 which ultimately responsible for increased MMP-1 formation **[59]**.

Articular chondrocytes mainly express MMP-13 that breaks down type II collagen and shows five to ten times more destructive effects to type II collagen than MMP-1 **[60]**. Apart from destructive effects on type II collagen, MMP-13 also destroys other matrix components like proteoglycan, osteonectin, perlecan, type IV and type IX collagen **[61]**.

MMP-9 levels are nearly undetectable in most of the cells but its expression can be increased in malignancy and inflammatory disorders like RA **[63]**. Expression of MMP-9 is stimulated by IL-1β and TNF-α. Apart from its degradation capacity of extra cellular matrix it can responsible for processing of TNF-α and IL-1β **[64, 65]**.

IL-1β increases the production of ADAMTS metalloproteinases by chondrocytes which causes proteolytic degradation of aggrecan molecules **[47]**. IL-1 stimulates prostaglandin E2 **[48]**. Synovial fibroblast cells & chondrocytes expressed prostaglandin E2. Prostaglandin H2 is converted to Prostagandin E2 with the help of the enzyme prostaglandin E synthase (PGES) **[66]**. Three different isoenzymes of prostaglandin E2 synthase are present: Microsomal prostaglandin E synthase 1(mPGES-1), Microsomal prostaglandin E synthase 2(mPGES-2) & cytosolic prostaglandin E synthase (cPGES) **[67]**. During RA, inflammation in the synovium causes activation of cyclooxygenase-II (COX-II) enzyme which ultimately causes induction of microsomal prostaglandin E synthase 1(mPGES-1) which catalyzes the formation of PGE2 **[68]**. PGE2 produces its variety of effects by acting through its receptors which are collectively known as EP receptors. EP receptors are rhodopsin type 7 alpha helical transmembrane G-protein coupled receptor **[67]**. Mainly 4 types of EP receptors are present: EP1, EP2, EP3& EP4 among which EP3 & EP4 receptors are mostly present in human body & PGE2 having higher affinity

to these receptors than EP1 & EP2 receptors **[69, 70]**. It has been seen that PGE2 by acting through the EP4 receptors produces some proinflammatory responses in RA. PGE2 signaling through EP2 receptors shows some anti-inflammatory properties and also responsible for proliferation of chondrocytes & cartilage regeneration. PGE2 induces apoptosis of chondrocytes in synovium by binding to EP4 receptors **[71]**. PGE2 signaling through EP4 receptors shows some important catabolic effects in cartilage like activation of matrix metalloproteinase, degradation of type II collagen & proteoglycan biosynthesis suppression **[72, 73]**.

IL-1β increases its own secretion by its autocrine activity as well as it increases the secretion of other cytokines like IL-6, TNFα, IL-8 **[74]**. During the progression of RA, reactive active species (ROS) production is stimulated by IL-1β. Reactive oxygen species (ROS) increases the generation of hydroxylated radicals, peroxides which ultimately responsible for cartilage destruction **[75]**.

The prime functions of synovial membrane are to prevent friction of joints by releasing synovial fluids which lubricate the surface of the joints, provide nutrition to the cartilage & provide joint support **[9]**. The synovial membrane consists of two layers: The intimal lining layer & sublining layer (subintima). The intimal layer is the superficial layer & faces towards the intra articular cavities. Synovial fluids are produced by the intimal layer & responsible for the lubricating properties to the joints. Macrophage like synoviocytes (Type A Synoviocytes) & fibroblast like synoviocytes or FLS (Type B Synoviocytes) are the two types of cells responsible for the production of intimal layer of synovial membrane **[9]**. Intimal layer having the thickness of 2-3 cells **[9]**. The sublining layer is made up of loose connective tissue, blood and lymph vessels, nerve fibers macrophages, mast cells, fibroblasts and T lymphocytes **[49]**. Hyperplasia of fibroblast like synoviocytes (FLS) is one of the crucial histopathological characterization of RA. IL-1 β produced by the activated macrophages responsible for the hyperplasia of FLS [10]. Hyperplastic FLS cells lack of apoptotic pathway **[11]**. The hyperplastic FLS characterized by increased expression of the MDM 4 protein that inhibits the activity of tumor suppressor gene p53which inhibits the activity of transcription factor p53 **[50]**. Hyperplastic FLS cells leads to the formation of pannus which causes bone erosion & cartilage destruction **[12]**.

A.3. Role of IL-1 receptor antagonist (IL-1ra) in RA:

IL-1ra is a type I & type II IL-1 receptor antagonist that is produced in the body. There are two types of IL-1ra: intracellular form (icIL-1ra) & secreted form (sIL-1ra)[76]. Activated macrophages & monocytes secretes sIL-1ra& during inflammation its secretion is increased whereas icIL-1ra mostly present in the epithelial cells **[77]**. Monocytes induces the expression of icIL-1ra mRNA **[77]**. IL-1ra binds to both type I & type II IL-1 receptors thereby block the signal transduction of IL-1α and IL-1 β. Although homology in amino acid sequence of IL-1ra &IL-1α is 30% and with IL-1 β is 19%, IL-1ra binding to both type I & type II IL-1 receptors does not activate the receptors to induce signal transduction **[78]**. It has been seen that binding capacity of IL-1ra to type I IL-1 receptors are more than IL-1 whereas binding capacity of IL-1ra to type II IL-1 receptors are less than IL-1 **[79]**.

Although IL-1ra are present in the RA synovium, their levels are significantly less than IL-1. Ratio range of IL-1 to IL-1ra of 3.6 to 1.2 is significantly less than the 10-to-100-fold excess in IL-1ra which is required to inhibit 50% biological activity of IL-1 **[80]**. Since activation of cellular response requires only 5% IL-1 receptor occupation by IL-1, a large amount of IL-1ra would be required therapeutically to inhibit inflammation induced by IL-1.

A.4. Role of IL-18 in RA:

IL-18 is a proinflammatory cytokine which can be detected in the arthritic synovium and in synovial fluids. It is mainly synthesized as precursor molecule pro IL-18 which is having 192 amino acid residues **[87]**. Pro IL-18 is converted to active protein IL-18 with 157 amino acid residues **[87]** with the help of the enzyme IL-1 β converting enzyme (Also known as caspase 1) **[81]**. Activated macrophages mainly secretes IL-18 **[82]**. Apart from macrophages, chondrocytes **[83]**, osteoblasts **[84]**, synovial fibroblasts **[85]** & keratinocytes **[86]** also secrete IL-18.IL-18 receptor having ligand binding chain known as IL-18Rα which binds with IL-18 with low affinity. Cells which express the beta chain of IL-18 receptors (IL-18Rβ) as coreceptor forms a strong affinitycomplex with IL-18-IL-18Rα.This complex actthrough toll/IL-1 receptor (TIR) domain and responsible for recruitment of MyD88, interleukin 1 receptor associated kinase (IRAKs), TNF receptor associated factor 6 (TRAF-6) and ultimately responsible for NFκB and other proinflammatory cytokine release. Binding capacity of IL-18 binding protein (IL-18BP)

to soluble IL-18 is much higher than IL-18Rα and inhibit binding of IL-18 receptor with IL-18. Thus IL-18-BP suppress the activity of IL-18 **[132]**.

IL-18 increases the secretion of TNFα, interferon gamma from Th1 cells & granulocyte-macrophage colony stimulating factor (GM-CSF) by natural killer cells (NK Cells) and T lymphocytes **[88]**. IL-18 expressed in the intimal lining layer & sublining layer (subintima) of the synovial membrane & activates macrophages produced by these lining layer. Activated macrophage releases various proinflammatory cytokines which is having pivotal role in articular cartilage destruction and inflammation. Synovial fibroblast & chondrocytes located proximity to the activated macrophages releases various inflammatory mediators & MMPs like MMP-13, MMP-3, MMP-1 **[89]**. IL-18 stimulates synovial cells & chondrocytes which results in increased production of iNOS, COX-2, PGE2, VEGF & IL-6 **[90, 91]**.

A.5. Role of IL-33 in RA:

IL-33 is an important member of IL-1 superfamily & having important role in the pathogenesis of various autoimmune & inflammatory disorders like RA. It is produced as 30-Kd precursor protein which is cleaved by caspase-1 to release active IL-33 with molecular weight 18-Kd **[92]**. IL-33 having its specific receptor known as ST2L which is mainly expressed in Th2 cells, NKT cells, eosinophils, basophils & in mast cells **[93-100]**. For signaling pathway of IL-33 mediated NFκB activation & cytokine production by Th2 cells, tumor necrosis factor receptor associated factor 6 (TRAF6) plays an important role as an adapter protein **[101]**. Expression of IL-33 in inflamed synovial membrane largely increased **[102]**. In collagen induced arthritis (CIA) model, ST2 expression is increased in the mast cells through which IL-33 produces its response.IL-33 causes activation of mast cells which leads to release of proinflammatory cytokines like IL-6 & IL-1β.IL-33 also stimulates CD4+T cells to release cytokines like IL-13 & IL-5. These cytokines cause B lymphocyte activation and antibody production which ultimately responsible for inflammation of articular joints and degranulation of mast cells **[103]**. Activated T cells and macrophages produces various proinflammatory cytokines that stimulates the release of IL-33 from macrophages which is a powerful chemoattractant to neutrophils **[104]**.

A.6. Role of IL-36 in RA:

IL-36, a member of the IL-1 superfamily, is an inflammatory cytokine.IL-36 consist of

three agonists: IL-36α, IL-36β and IL-36γ, and IL-36 receptor antagonist (IL-36Ra). The encoding genes for the protein family IL 36 are located on human chromosome 2 **[105]**. In order to obtain their complete agonist or antagonist function, IL-36 α, β, γ and IL-36Ra cytokines need to be processed. IL-36 Ra does not have antagonistic potential in its native form; similarly, IL-36 α, β and γ are 100-1000 times less active than their refined counterparts **[108]**. Neutrophils releases various enzymes like elastase, cathepsin G (Also known as Cat G) & proteinase-3 which are responsible for IL-36α, IL-36βand IL-36γ activation and processing. Elastase or Cat G cleaves at alanine 4 &lysine 3 position of inactive IL-36α respectively and causes formation of activated IL-36α **[109]**. Cat G cleaves at arginine 5 (Arg5) to produce activated IL-36β. Elastase or proteinase-3 cleaves at the position of Valine 15 to produce activated IL-36γ from IL-36γ precursors **[109]**. IL-36Ra precursors converted to activated IL-36Ra neutrophil elastase **[110]**.

IL-36 cytokines are expressed in the synovial tissue of RA patients by different cells: plasma cells, macrophages and to a lesser degree, fibroblasts, endothelial cells and dendritic cells **[106, 107]**. IL-36 α, IL-36Ra & IL-36 receptors (IL-36R) are expressed in the synovium of RA patients and also found that expression of IL-36 α is higher in RA than osteoarthritis **[111]**. During inflammatory response in CIA model in mice, gene expression of IL-36 α, IL-36β, IL-36Ra & IL-36 receptors (IL-36R) is increased **[112]**. IL-36R expressed on FLS cells of synovial membrane which on binding with IL-36 activates FLS cells to produce variety of inflammatory cytokines like IL-6 & IL-8 & MMPs **[113]**. IL-36 γ helps in differentiation of T lymphocytes and release of IL-9 from lymphocytes (Th9) **[114]**, which helps in increased survival of neutrophils and enhanced differentiation of Th17 cells in the synovium **[115]**. Synovium and peripheral blood of inflammatory arthritic patients having increased levels of Th9 cells **[116]** which correlates with the disease progression in RA **[115]**. IL-36 and IL-36R can stimulate dendritic cells & helps in the maturation of dendritic cells. Dendritic precursor cells on exposure to IL-16 releases IL-12 and helps in T cell to Th1 cell differentiation. IL-36β having a stimulatory effect on Th1 effects **[117]**. However, it has been seen that magnitude of the stimulatory responses of IL-36 in chondrocytes and fibroblast like synoviocytes (FLS) are marked lower than that of IL-1 which indicates that IL-36

probably the main inflammatory cytokine in human RA **[118]**.

IL-36Ra plays an important antagonistic role in IL-36 mediated cytokine release and shows an antagonistic effect on various inflammatory disorders like RA and crohn's disease **[22]**. IL-36Ra blocks IL-36R by inhibiting IL-1RAcP recruitment. At the same time single immunoglobulin IL-1R-related molecule (SIGIRR) recruited by IL-36Ra which inhibits TIR domain to produce antagonistic effects **[22, 23]**.

A.7. Role of IL-37 in RA:

Interleukin-37 (IL-37) was first found and recognized by Kumar *et al*. in 2020 through computational sequence analysis **[124]**. Nold *et al*. identified that IL-37 could inhibit innate immune response **[125]**. The human IL-37 gene has a length of 3,617kb and located in chromosome 2 **[126]**. FiveIL-37 isoforms have been identified: IL-37a, IL-37b, IL-37c, IL-37d & IL-37e which are encoded by six exons **[126]**. All IL-37 isoforms produced as precursor molecules which upon cleavage by caspase-1 converted to active forms. Cleavage site of caspase-1 is located between amino acid residues (D20 & E21) expressed by exons **[127]**. Caspase-1 mutation inhibits the translocation of IL-37 into nucleus to form complex with Smad3 gene (Mothers against decapentaplegic homolog 3) which responsible for downregulation of transcription of some key genes **[127]**. Binding of IL-37 to IL-18 α facilitates IL-1R8 recruitment instead of IL-18R β **[128]**. Tyr 536 & Ser447 residues are absent in toll/IL-1 receptor (TIR) domain of IL-1R8.Binding of TIR domain of IL-1R8 to MyD88 results in inadequate signal transduction and formation of multiple signaling that inhibits the inflammatory reactions **[128]**.

IL-37 can be found in many tissues, but level of expression in healthy human tissue is poor **[125]**. Tissue specificity is the characteristics of IL-37 expression. Thymus glandular cells, lungs, liver, colon, uterus, natural killer cells, activated B lymphocytes mainly express IL-37a, IL-37b& IL-37c whereas testis & bone marrow mainly express IL-37d and IL-37e.Brain only express IL-37a, Kidney only express IL-37b and heart only express IL-37c **[126]**.

Elevated levels of IL-37 can be detected in plasma and synovial tissue of RA patients but it is nearly undetectable in healthy individuals **[125]**. Decreased levels of IL-37 can be detected in the patients with remissive state of RA compared to active cases of RA. Recombinant IL-37 administered by intra-articular injection in streptococcal induced arthritic model **[129]** in mice or in collagen

induced arthritic model **[130]** in mice causes downregulation of Th17 cytokine & IL-17 production and improves symptoms of RA. IL-37 also decreases the expression of IL-1 β, IL-6.IL-37 also have an inhibitory effect on Th17 proliferation but don't have any significant role in differentiation of Th17 cells **[130]**. Apart from these, IL-37 inhibits osteoclast formation (osteoclastogenesis) mediated by RANKL and also inhibits bone resorptive action of osteoclast cells **[131]**. It has been seen that IL-37 binds to IL-18R because IL-37 having some homology in amino acid sequence with IL-18 (Lys-124 & glucoses-35). Binding of IL-37 to IL-18Rα recruits IL-IR8 to produce IL-37/ IL-18Rα/ IL-IR8 complex which blocks the activity of IL-18 **[133]**.

A.8. Role of IL-38 in RA:

The newest IL-1 family member is IL-38. Four exons of IL-38 gene are located on chromosome 2q13-14.1 in cluster of IL-1 family gene [14]. IL-38 gene located in close proximity of IL-36Ra gene (IL-36RN) and 49,479 base pair upstream from IL-1Ra gene (IL-1RN) **[123]**. IL-38 precursor protein having molecular mass of 16.9kD and having 152 amino acid sequence **[15]**. It has been seen that caspase-1 cleavage site and signal peptide is absent in IL-38 **[16, 124]**. IL-38 shares 41% amino acid sequence homology with IL-1Ra gene and 43% with IL-36Ra gene **[17, 124]**. However, IL-38 having 14-30% amino acid sequence homology with IL-1β and other cytokines of IL-1 superfamily.

IL-38 having important role in inhibition of various proinflammatory cytokine signaling pathways by binding with various receptors like IL-1R1 (interleukin-1 receptor 1), IL-36R (interleukin-36R) and IL-1RAPL1 (interleukin-1 receptor accessory protein-like 1) thereby regulates the functions of various mononuclear cells, macrophages and T lymphocytes. IL-1RI is an IL-1R family member which comprises of IL-1R1 to IL-1R10.Binding of IL-1 to IL-1R1 results in activation of the receptor and leads to formation of interleukin-1 receptor 1 (IL-1R1)-interleukin-1 receptor accessory protein (IL-1RAcP) complex. IL-1R1-IL-1RAcPcomplex recruits myeloid differentiation primary response 88 (MyD88) through TIR domain which further activates NF-$_K$B pathway and mitogen activated protein kinase (MAPK) pathways. MAPK pathway act through p^{38}, extracellular regulated protein kinases (ERK) 1/2 and c-Jun N-terminal kinase (JNK) which ultimately responsible for activator protein-1 (AP-1) activation. AP-1 and NF-$_K$B stimulates proinflammatory cytokine production by binding with specific genes

[20, 21]. IL-1Ra blocks recruitment of IL-1RAcP and recruits inhibitory receptor single immunoglobulin IL-1R-related molecule (SIGIRR) that inhibit the cytokine release pathways. As IL-38 shares 41% amino acid sequence homology with IL-1Ra, it indicates that IL-38 might have similar anti-inflammatory property of IL-1Ra **[17]**. However, it has been seen that IL-38 having affinity to IL-1R1 but the affinity is much lower compared to IL-1 and IL-1Ra **[17]**.

Apart from IL-1R1, IL-38 also act as an antagonist to IL-36R. IL-36 binds to IL-36R and activate it. Activation of IL-36R causes recruitment of interleukin-1 receptor accessory protein (IL-1RAcP) which forms cytosolic toll-interleukin 1 receptor (TIR) domain **[18]**. IL-1R1-IL-1RAcP complex recruit myeloid differentiation primary response 88 (MyD88) through TIR domain which ultimately responsible for release of various proinflammatory cytokines like TNF-α, IL-17, IFN-γ **[19]**. IL-38 inhibits the binding of IL-36 to IL-36R as well as recruitment of interleukin-1 receptor accessory protein (IL-1RAcP) therefore prevent the release of various proinflammatory cytokines.

IL-38 also act on IL-1RAPL1 (interleukin-1 receptor accessory protein-like 1) receptor. It is an orphan receptor characterized by presence of intracellular toll/IL-1 receptor (TIR) domain and three extracellular immunoglobulin domains **[20]**. It has been seen that JNK/API pathway is activated by IL-1RAPL1 **[24]**. Full length IL-38 on binding with IL-1RAPL1 increases the production of IL-6 by activating JNK/API pathway whereas truncated IL-38 on binding with IL-1RAPL1 inhibit activation of Th17 cells which responsible for decreasing the release of IL-8 and IL-6 that ultimately decreases activation of macrophages **[25]**.

IL-38 have important anti-inflammatory effects on autoimmune disorders like RA. Apart from Th1 and Th2 cells, a novel subtype of T lymphocyte has been identified which was named Th17 cells because of its capacity to express IL-17. The most important difference between Th17 cells and other T cells is that Th17 cells can express IL-22 and IL-17 **[135, 136]**. In various studies it has been seen that Th17 cells having direct involvement in the pathogenesis of various autoimmune disorders like RA, psoriasis, inflammatory bowel disease etc. **[137]**. mRNA expression of IL-38 significantly increased in CIA model **[113]**. Adeno-associated virus -IL-38 (AAV-IL-38) injected to mice of CIA model showed significant reduction of expression of various proinflammatory cytokines released

from Th17 cells (IL-22, IL-17, IL-23), chemokines etc. **[138]**. Clinical score and severity of RA decreases significantly in AAV-IL-38 treated mice of CIA model. After AAV-IL-38 treatment, density of macrophages in the inflamed synovial area significantly decreases **[138]**. IL-38 also downregulate the expression of TNFα, IL-10 levels. when IL-38 knock out mice induced K/BxN model of RA, expression of IL-6, IL-1β in the joint significantly increased compared to control group of mice which indicates the role of IL-38 in the reduction of IL-6, IL-1β expression **[139]**.

B. Role of TNF-α in RA:

An important signaling protein in adaptive and innate and immune response is tumor necrosis factor-alpha (TNF-α). It is having important role in the regulation of development of embryo, formation of germinal center, sleep-wake cycle etc. Apart from these, TNF-α responsible for release of various proinflammatory cytokines and enhancement of adhesion and permeability of lymphocyte, monocyte, neutrophil at the site of inflammation **[140, 141]**. Macrophages are mainly responsible for release of TNF-α. However, apart from macrophages, B lymphocytes, some types of T lymphocytes, natural killer cells, fibroblasts also release TNF-α at low level **[142, 143]**. Human TNF-α gene located on chromosome 6. 1.7kb messenger RNA codes for TNF-α. Initially 26-kDa membrane bound TNF- α (mTNF- α) with 233 amino acid sequence produced. Soluble TNF-α (sTNF- α) with molecular weight of 17kDa is produced from mTNF- α by TNF-α converting enzyme **[144, 145]**. TNF-α converting enzyme cleaves mTNF- α at C-terminal domain of extracellular region to produce sTNF- α with 157 amino acids.

Two different types of TNF-α receptors have been identified which are responsible for TNF-α mediated signal transduction. Both tumor necrosis factor- receptor 1 (TNF-R1) and tumor necrosis factor- receptor 2 (TNF-R2) are transmembrane receptors with equal size of intracellular and extracellular domain and with a single transmembrane chain. Gene encoding for TNF-R1 located on chromosome 12p13. TNF-R1 having approximate molecular weight of 55-60kDa and composed of 455 amino acid sequence whereas, gene encoding for TNF-R2 located on chromosome 1p36. TNF-R2 having approximate molecular weight of 70-80 kDa and composed of 461 amino acid sequence. In almost all cells in human body TNF-R1 is expressed and can be activated by both sTNFα and mTNFα whereas, TNF-R2 mainly expressed in T cells, microglia, oligodendrocytes and endothelial cells **[146]**.

TNF-R2 is fully activated by mTNFα only. On binding with TNF-R2, mTNFα produces stable complex to dissociate **[147]**. STNFα shows low affinity towards TNF-R2 and results in weak signal transduction **[148]**.

There are numerous proinflammatory responses are present which are exerted by TNF-α. In the patient with RA TNF-α can be detected in both synovial tissue and synovial fluid **[149]**. Apart from these, In the cartilage-pannus junction TNF-α can be detected which indicates its association in degradation of cartilage **[150]**. Though the factors that increases TNFα release from inflamed synovium is not properly known, recent studies indicate that IL-15 can be a potential candidate for stimulating the release of TNFα from inflamed synovium **[151]**. There is significant proof that TNF-α has a pathogenic role in synovitis **[152]**. TNF-α increases the expression of various adhesion molecules like intracellular adhesion molecule 1(ICAM 1), endothelial leukocyte adhesion molecule (ELAM-1), vascular cell adhesion molecule 1(VCAM 1) which act as chemoattractant to inflammatory cells like monocytes and neutrophils, resulting in aggregation of inflammatory cells in the synovium **[153]**. TNF-α stimulates proliferation of synovial cell lining which leads to formation of synovial hyperplasia **[153]**. Stimulation of synovial cell lining by TNF-α results in production of various proinflammatory cytokines like IL-1, GM-CSF and various types of MMPs like collagenase, stromelysin which ultimately leads to destruction of cartilage in RA **[153]**. Stimulation of synovial cell lining by TNF-α also responsible for formation of PGE_2 which involved in generation of pain **[154]**. Administration of anti-TNF-α monoclonal antibody to TNF-α over expressed mice with RA shows significant prevention of disease indicating potential role of TNF-α in RA **[8]**. Inhibition of synovitis can be detected in CIA model by the administration of anti-TNF-α monoclonal antibody also indicates potential role of TNF-α in RA **[155]**.

CONCLUSION

RA is a progressive degenerative disorder of joints which is characterized by severe synovial inflammation and degradation of cartilage. Apart from the catabolic effects of various pro inflammatory cytokines various anabolic anti-inflammatory cytokines also expressed. Dysregulation of balance between proinflammatory and anti-inflammatory cytokines responsible for articular cartilage destruction in RA. Various types macrophage derived proinflammatory cytokines like IL-1α, IL-1β, IL-18, IL-33, IL-36 (α, β & γ) & TNF- α shows numerous inflammatory

response that ultimately responsible for cartilage destruction in RA. In this article impact of various macrophage derived pro and anti-inflammatory cytokines on RA have been discussed. Authors of this article tried to summarize the important information regarding the role of macrophage derived pro & anti-inflammatory cytokines in the pathogenesis of RA.

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